Docket No.:PF-0346-1 DIV
Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1644

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GND

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By: _____ Printed: Katherine Stofer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hillman et al.

Title: T-CELL RECEPTOR PROTEIN (AS AMENDED)

Serial No.: 09/405,940 Filing Date: September 27, 1999

Examiner: Ewoldt, G. Group Art Unit: 1644

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Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed June 28, 2001, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a one-month extension of time in order to file this Brief. Authorized fees include the statutory fee of $110.00 for a one-month extension of time, as well as the $320.000 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, and 13 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.) (Reel 8648, Frame 0077), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 2, and 13
Claims allowed:	(none)
Claims canceled:	Claims 3-12
Claims withdrawn:	24-26
Claims on Appeal:	Claims 1, 2, and 13 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a susbstantially purified polypeptide,TCRLP (SEQ ID NO:1), a variant thereof having at least 90% amino acid sequence identity to SEQ ID NO:1, and a composition comprising SEQ ID NO:1 (specification, p. 3). TCRLP is described as a new T-cell receptor beta-like protein based on a high degree of sequence identity with known T-cell receptor beta proteins (82-85% identity, specification,p. 14). T-cell receptors are described in the specification and art of record as functioning in antigen recognition in cells and in the transmission of activation signals to initiate cell-mediated immune reactions. Genes activated in these processes produce a variety of

secreted factors that induce turmoricidal and anti-inflammatory activities. Defects in T-cell receptor genes are described as involved in various cancers (e.g., lymphomas and leukemias), allergic responses, and autoimmune and immuodeficiency disorders (specification, pp. 1-2). Northern analysis shows the expression of TCRLP primarily in fetal tissues and immune cell libraries (specification, p. 14). The claimed protein, and compositions thereof, are therefore useful in the diagnosis, prevention, and treatment of cancer and autoimmune disorders, in the development of drugs to treat these disorders, and in the assessment of drug safety and efficacy, e.g., toxicology testing (specification, pp. 14, 26-27, 32, and 35).

(6) THE FINAL REJECTION

Claims 1, 2, and 13 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that:

- the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicant asserts a utility of the protein encoded by SEQ ID NO:1 as a pharmaceutical composition for the treatment or prevention of diseases ranging from autoimmune disorders to cancer, however that --- [t]he utilities are premised on the similarity of the disclosed full length protein (SEQ ID NO:l) to a human T cell receptor beta chain taught by prior art. However, there is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art to believe said identity gives a credible use to the claimed protein. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function (Mikayama et al.). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell (Voet et al.).

Claim 2 stands rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor, at the time the application was fled, had possession of the claimed invention. The rejection alleges in particular that:

- there is insufficient written description to show that Applicant was in possession of any variant of a peptide encoded by SEQ ID NO:1. Variant has not been defined in the specification, however "altered sequence" is defined to include peptides with any and all insertions, substitutions, and deletions, i.e., any peptide or protein. Variant is considered to include at least all "altered peptides", thus, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See Eli Lilly, 119 F.3d 1559, 43 USPQ2d 1398.

(7) ISSUES

1. Whether claims 1, 2, and 13 directed to a T-cell receptor polypeptide sequences meet the utility requirement of 35 U.S.C. §101, e.g., whether there is evidence that an 85% correlation between the amino acidsequence of the claimed protein and a T-cell receptor beta protein, a protein known to have utility, demonstrates a "substantial likelihood" of utility under 35 U.S.C. § 101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether claim 2 directed to a polypeptide having at least 90% amino acid sequence identity to SEQ ID NO:1 and which retains the biological activity of a T-cell receptor polypeptide is sufficiently described in the specification to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

(8) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

Claim 2 stands alone.

(9) APPELLANTS' ARGUMENTS

The rejection of claims 1, 2, and 13 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as a T-cell receptor polypeptide, is a polypeptide sequence encoded by a **gene** that is expressed in humans, in particular, in fetal tissues and imune cell tissues. The novel polypeptide is demonstrated in the specification to be a member of the class of T-cell receptor polypeptides, whose biological functions include the induction of tumoricidal and anti-inflammatory activity and which play a role in autoimmune and immunodeficiency disorders. See specification, p. 2. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. The claimed invention can als be used as a marker for certain cancers (e.g., lymphoma and leukemia), allergic responses and autoimmune and immunodeficiency disorders (specification, p 2, lines 26-28, and reference # 6 of the IDS).

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. TCRLP is, in that regard, homologous to two human T-cell receptor polypeptides that are both essential components of a T-cell receptor complex. In particular, TCRLP shares more than 80% sequence identity over 314 amino acid residues, and is in fact nearly 100% identical with the two proteins in the C-terminal half of the protein (about 150 amino acid residues) . See specification, p. 14, and Figures2A and 2B.

This is more than enough homology to demonstrate a reasonable probability that the utility of the human T-cell receptor polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998).

Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human T-cell receptor polypeptide is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Appellants submit with this brief the declaration of Mr. L. Michael Furness (the Furness Declaration }describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate. (Furness at ¶ 11).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v.*

> *Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*,

51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The diagnosis and treatment of cancer and autoimmune disorders are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the accompanying Furness declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed TCRLP is functionally related to a T-cell receptor beta polypeptide, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellant need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the claimed polypeptide shares more than 80% sequence identity over 300 amino acid residues with T-cell receptor beta polypeptide. See specification, p. 14. It is also apparent from Figures 2A and 2B of the specification that TCRLP is nearly100% identical in the C-terminal half of the molecule to the knowm homologs.

This is more than enough homology to demonstrate a reasonable probability that the utility of the T-cell receptor beta polypeptide can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., *supra*). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to T-cell receptor beta is, accordingly, very high.

The Examiner must accept the applicants' demonstration that the homology between the claimed invention and the T-cell receptor beta polypeptide demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. See Mikayma et al.(1993), Voet et al.(1990), Bork (2000), Atwood (2000), and Skolnick et al.(2000), in Office Actions, filed 10/24/00 and 4/04/01. Importantly, none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well (see Response to Office Action, filed 1/24/01, p. 4-5). At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of the T-cell receptor polypeptide family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the the T-cell receptor polypeptide family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the the T-cell receptor polypeptide family, useful.

B. The use of TCRLP for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

In his Declaration, Dr. Furness explains the many reasons why a person skilled in the art who read the Hillman '097 appplication on July 18, 1997 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 11-15). Much, but not all, of Dr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Dec. at ¶ 11.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Dr. Furness explains:

> In view of the Hillman '097 application . . . and other related pre-July 1997 publications, persons skilled in the art on July 18, 1997 clearly would have understood the Hillman '097 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . .
> * * *
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer and autoimmune disorders, for such purposes as evaluating their efficacy and toxicity.

Dr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins at 26).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, 29 Xenobiotica No. 7, 655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et. al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Genesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

The more genes -- and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to the undersigned, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information

database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the Wall Street *Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), **in particular genes having medical and pharmaceutical significance such as the instant sequence.** (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific

community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific, substantial, and credible" utilities. (Office Action filed 10/24/00, p. 3). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is

not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptide is a member of T-cell receptor protein family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the T-cell receptor protein family to TCRLP. In the Examiner's rejection, the

Patent Examiner takes the position that unless appellants can identify which particular biological function within the class of T-cell receptor protein family is possessed by TCRLP, utility cannot be imputed (Office Action, filed 10/24/00, p. 4). To demonstrate utility by membership in the class of T-cell receptor proteins, it would appear that the Examiner would require that all T-cell receptor proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses TCRLP as if the general class in which it is included is not the T-cell receptor protein family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the T-cell receptor protein

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

family does not. The T-cell receptor protein family is sufficiently specific to rule out any reasonable possibility that TCRLP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the T-cell receptor protein class of growth factors has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the T-cell receptor protein, TCRLP (SEQ ID NO:1) is also useful.

C. The use of TCRLP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Examiner rejected the claims at issue on the grounds that the use of an invention as a tool for research is not a "substantial" use, e.g., that "Basic research such as studying the properties of the claimed product itself or mechanisms in which the material is involved would be required" (Office Action, filed 10/24/00, p. 4). Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further

research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness declaration. The Furness declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: screening libraries of pharmaceutical agents to identify those which specifically bind TCRLP in a variety of drug screening techniques; generating antibodies which specifcally bind and can identify TCRLP; and titration of TCRLP to initially determine the effective dose in cell culture assays or in animal models.

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its 80-85% homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.A., *supra*, the literature cited by the Examiner is not inconsistent with the applicants' proof of homology by a reasonable probability. It may show that applicants cannot prove function by homology with **certainty**, but applicants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

In the present case, the Office Action alleges that the amino acid sequence identity between TCR:LP and known T-cell receptor proteins is insufficient to establish that TCRLP is a member of the T-cell receptor family of proteins because "there is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art to believe said identity gives credible use to the claimed protein" (Office Action, filed 10/24/00, p. 3). The Examiner attempted to support this assertion with the teachings of Mikayma et al.(1993), Voet et al.(1990), Bork (2000), Atwood (2000), and Skolnick et al.(2000), all of which are of record and are addressed in turn below. However, all of these documents fail to support the outstanding rejections.

The Examiner cites Mikayama et al. as evidence that a single amino acid residue difference between two proteins (here, MIF and GIF) can lead to differences in function. MIF and GIF, however, are not different proteins. MIF and GIF have been shown to be encoded by identical genes and thus to have identical amino acid sequences. Watarai, H. et al. (2000; Proc. Natl. Acad. Sci. USA 97:13251-13256) state that "[g]lycosylation inhibiting factor (GIF) and macrophage migration inhibitory factor (MIF) share an identical structure gene." (See abstract, page 13251.) Further, Watarai et al. state that "[a]fter molecular cloning of this cytokine [GIF], however, we realized that the sequence of the coding region of human GIF cDNA (6) was identical to the sequence of human MIF cDNA (7), except one base. In the human genomes, Paralkar and Wistow (reference #8 of Watari et al.)

identified only one functional MIF-like gene, whose predicted transcript sequence agreed exactly with that of MIF cDNA, indicating that the one base difference between GIF and MIF cDNA is due to an error in sequencing." (See page 13251, column 1, first paragraph.) It is noted that the Watarai et al. paper is from the some of the same authors (Kimishige Ishizaka, Yasuyuki Ishii) as the Mikayama paper. The differences in activity between MIF and GIF have been shown to result from differences in post-translational modification, not in sequence, though both indeed function as cytokines. Hence, the Examiner's use of Mikayama et al. as a document purporting to show that single amino acid differences result in differences in function is incorrect. It is noted in any case that changes in function of proteins due to post-translational modifications and/or single amino acid substitutions are far and away the exception, not the rule, and one of skill in the art would not reasonably doubt the asserted imputed utility of TCRLP based on its similarity with human T-cell receptor beta protein.

Likewise, the Examiner's citation of Voet et al. and the fact that a single amino acid change in hemoblobin causes sickle-cell anemia is again a case of the exception not the rule. The fact that the sickle-cell mutation has been perpetuated is a fluke of nature due only to the fact that it confers an advantage (immunity to malaria) in heterozygous carriers. Generally, without such coincidence, the sickle-cell gene would have been selected against, because it causes a disease that disadvantages the carrier. Without this extraordinary twist of fate, the mutant gene would have been eliminated many generations ago. One can hardly expect this sort of serendipity to be a frequent occurrence, "rescuing" genes with mutations in key functional areas that would otherwise be eliminated. In the present case, for TCRLP, there is absolutely no reason to assume that the protein of SEQ ID NO:1 possesses any mutation in a key functional region (and it is the Examiner's burden in any case to show that this is more likely than not).

The Examiner further relied on the teachings of Bork, Atwood and Skolnick et al. regarding the alleged unpredictability of current methods of compartive sequence analysis. Applicants respectfully suggest that the Examiner attempts to draw too sweeping a conclusion from Bork, Atwood, and Skolnick et al. It may be true that the use of sequence analysis to predict protein function is not 100% percent accurate (although still, based upon Bork's figure of 70% accuracy, more likely than not to be

correct) as the quality of data in the public sequence databases is still insufficient to annotate perfectly every new sequence. However, this is a general conclusion; one of skill in the art would clearly understand that the likelihood of a prediction being correct for a particular sequence depends upon how much data is available for the particular family to which it belongs.

The Examiner's reference to Atwood teaching a error rate >80% in predicting protein structure/function appears to be drawn from the following statement:

> In "predicting" genes, protein functions, and structures, it is helpful to define our terms precisely and be honest about our achievements. Otherwise, we will continue to be baffled by paradoxical new prediction methods that yield >80% error rates. (Atwood, page 473, first column.)

Atwood's statements (and indeed the entire Atwood document) mention several types of prediction analysis, that of genes, protein functions, and structures. Atwood does not specify which are the "paradoxical new prediction methods" that yield the ">80% error rates" and whether these rates apply to predictions of genes, protein function, or structures, or to some or all of the above. Indeed, Atwood does not describe **any** error rate for the method used in the present application (e.g., BLAST analysis) to ascribe T-cell receptor activity to TCRLP based on sequence similarity to a human T-cell receptor beta protein.

The Examiner also draws too sweeping a conclusion from the statements in the Skolnick et al. document. Careful reading of the statements that the Examiners quotes and paraphrases shows the lack of applicability to the instant invention. First, Skolnick et al. state, with respect to the use of sequence analysis to predict protein function, that "[b]oth the alignment and the motif methods are powerful but a recent analysis has demonstrated their significant limitations[15], suggesting that these methods will increasingly fail as the protein-sequence databases become more diverse." The Examiner has not shown, and Skolnick et al. do not assert, that the methods used in the present application to ascribe T-cell receptor activity to TCRLP based on sequence similarity to a human T-cell receptor beta protein result in mis-analysis of the claimed polypeptide sequences and indeed that any alleged "limitations" outweigh the "powerful" nature of the methods. The Examiner quotes Skolnick et al. that "inaccurate use of the sequence-to-function" methods has led to significant functional-annotation errors

in the sequence databases." However, the Examiner provides no evidence that any "inaccurate use of the sequence-to function methods" was made in the present invention. Again, sweeping conclusions, without any analysis of the data actually present in the instant application, do not constitute either evidence or sound scientific reasoning to show that a person of ordinary skill in the art would reasonably doubt Applicants' invention lacked patentable utility.

The Board's attention is further directed to Brenner et al., *supra* that teaches through exhaustive analysis of a data set of proteins with **known** structural and functional relationships and with **<40%** overall sequence identity, that 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) As shown in the Figures and as discussed in the specification, SEQ ID NO:1 shares 80-85% identity with at least two known T-cell receptor beta proteins over at least 300 residues, and nearly 100% identity over 150 residues, vastly exceeding this threshold. Since these criteria are based on a data set of known homologous proteins with shared structural and functional features, one of ordinary skill in the art would reasonably expect the polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of a T-cell receptor beta protein.

This assertion is further supported by the teachings of Bowie et al. (Response to Office Action, filed 1/24/00, Exhibit 2). Bowie teaches that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among Applicant's polypeptide and the known T-cell receptor proteins, are likely to occur at positions of minimal functional

importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Applicant's polypeptide and the two known human T-cell receptor proteins is indicative of a common function, and hence common utility, among these proteins.

The preponderance of evidence therefore does not support the Examiner's basis for the rejection of claims under 35 U.S.C. § 101. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the T-cell receptor family of proteins, which are known to have specific utility.

III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was

determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

IV. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(10) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the

claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The rejection of claim 2 under 35 U.S.C. § 112, first paragraph is improper as the claimed genus of polypeptides is sufficiently defined by both structural and functional limitations.

The Examiner has stated that the term "variant" as recited in claim 2 is considered to include at least all "altered peptides" peptides as defined in the specification to include peptides with any and all insertions, substitutions and deletions, i.e., *any* peptide or protein. Therefore that one skilled in the art would conclude that the specification fails to describe the claimed genus. See Eli Lilly, 119 F.3d 1559, 43 USPQ2d 1398.

The Examiner's interpretation of the term "variant" to include all "altered peptides" is clearly unjustified as the claim specifically recites "A variant --- having at least 90% amino acid identity of SEQ ID NO:1 and which retains IL-2 inducing activity". Clearly this would not encompass *any* peptide or protein. Furthermore the recitation of "at least 90% amino acid identity" and a specific biological activity meets the requirements of an adequate written description of a genus as described in Lilly (supra) that ---- an adequate description of a genus may be achieved by means of a disclosure of a representative number of polynucleotides ----- or by recitation of structural and functional features common to members of the genus which features constitute a substantial portion of the genus (emphasis added). The limitations of "90% amino acid identity" and "IL-2 inducing activity" constitute strucutural and functional features that represent the entirety of the claimed genus, and therefore meet these guidlines. Applicants therefore respectfully reqeuest withdrawal of the rejection of claim 2 under 35 U.S.C. § 112, first paragraph.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

Respectfully submitted,

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